

Overview of the Above Amendments:

Claim 1 has been amended to recite that the adjuvant composition "is capable of increasing the immune response to an antigen when administered with the antigen." New claim 37 has been added which recites that the composition further comprises a selected antigen. Support for the amendment and new claims can be found throughout the specification at, e.g., page 4, lines 30-31; page 24, lines 15-18; page 25, lines 7-13; page 28, lines 5-6; and in the examples.

Thus, no new matter has been added to the application by way of the amendment and the new claim.

Rejections Over the Art:

Claims 1, 5, 6 and 9 were rejected under 35 USC §102(b), as anticipated by Idson, B. "Pharmaceutical Emulsions" in *Pharmaceutical Dosage Forms*, Vol. 1 (Lieberman et al., eds.) Marcel Dekker, New York, pp 199-243, 1988 ("Idson"). The Office asserts that Idson relates to submicron parenteral nutrition preparations that fall within applicants' claims and argues that the term "adjuvant" as it previously appeared in the claims did not carry "patentable weight because the recitation occurs in the preamble." Office Action, page 2. Applicants have now recited in the body of claim 1 that the adjuvant composition "is capable of increasing the immune response to an antigen when administered with the antigen." Since Idson does not disclose a preparation that acts as an immunological adjuvant as embodied by applicants' claims, the amended claims are believed to clearly distinguish over this reference.

With respect to the Office's comment regarding the term "comprising," Idson does not disclose an adjuvant

composition falling within applicants' claims. Accordingly, the fact that other elements in Idson might be present in applicants' composition is irrelevant. Based on the foregoing, the rejection over Idson is believed to be overcome.

Claims 1, 5, 6 and 9 were also rejected under 35 USC §102(b), as anticipated by U.S. Patent No. 4,647,586 to Mizushima et al. ("Mizushima"). The Office asserts that Mizushima "discloses pharmaceutical compositions that comprise an oil-in-water emulsion containing a metabolizable oil and a phospholipid emulsifier and do not include polyoxypropylene-polyoxyethylene block copolymer or muramyl peptides." Office Action, page 3. The Office argues that applicants' previous arguments with regard to Mizushima are not persuasive because "the term 'adjuvant' has not been given patentable weight because the recitation occurs in the preamble." Office Action, page 3. As explained above, the recitation that the adjuvant composition "is capable of increasing the immune response to an antigen when administered with the antigen" has been inserted into the body of claim 1. Mizushima does not describe an adjuvant composition, nor are Mizushima's formulations related in any way to vaccines. Accordingly, applicants' invention also patentably distinguishes over Mizushima.

Additionally, as with Idson above, the use of the term "comprising" does not bring applicants' invention within the purview of Mizushima since Mizushima does not disclose adjuvant compositions. Accordingly, the rejection over Mizushima is also believed to be overcome.

The Office maintained the rejection of claims 1-9, 29 and 36 under 35 USC §103(a), as unpatentable over U.S. Patent No. 5,109,026 to Hoskinson et al. ("Hoskinson") and U.S. Patent No. 3,919,411 to Glass et al. ("Glass") in view

of Idson and Remington's *Pharmaceutical Sciences* (Gennaro, ed.) Mack Publishing Co., Pennsylvania, pp. 298-299, 317-321 and 1507-1511, 1985 ("Remington"), for reasons of record.

As with those rejections stated above, the Office notes that the term "comprising" does not preclude addition of other components to applicants' compositions and that the recitation of "adjuvant" previously only in the preamble, did not carry patentable weight. Furthermore, in maintaining the rejection, the Office has disputed the sufficiency of the Declaration submitted with the previous response, arguing that although the Declaration presents data with respect to a formulation falling within the scope of the claims (termed "MF59"), "the demonstration of adjuvant activity for a single submicron composition is not commensurate in scope with the claims that encompass compositions with different oils and emulsifying agents in varying amounts." Office Action, page 6.

However, the Declaration was provided to rebut the previous Examiner's allegations that applicants' compositions acted by the same mechanism as the Glass compositions. Specifically, in making the rejection, the Office had questioned applicants' arguments with respect to rapid dispersal and asserted that "depot effects from Glass et al. and from Applicants are likely to be comparable." Paper No. 38, page 3. Applicants provided evidence in the Declaration that a composition falling within the scope of the claims did not act by this mode of action. This evidence indeed bolsters applicants' assertions that the compositions described by Glass are not analogous to applicants'.

First of all, as previously explained, Glass uses a macromolecular synthetic resin which traps an antigen at the injection site. This mechanism is widely used in the art

and is essentially a variation on incomplete Freund's adjuvant (IFA) with the addition of a synthetic matrix to bind antigens for slow release. In fact, Glass describes an adjuvant as a "substance that operates as a binder, carrier, or suspending vehicle for immunogens...the function of which is to increase the effectiveness of the agent or the immunogenic response from an immunogenic agent by virtue of the retardation and slowing down of the absorption of such immunogens...into the host's system..." Column 1, lines 46-54. On the other hand, applicants' compositions, by virtue of the unique combination of elements and the submicron particle size, are able to rapidly disperse both the antigen and the adjuvant from the site of administration. Both the Declaration and Ott et al., provided with the previous response, contradict the Office's suggestion that applicants' compositions work through some sort of depot effect and are therefore analogous to the Glass compositions. Applicants again request that should the Examiner be basing this assertion on facts within her personal knowledge, that an affidavit be provided as required by 37 CFR §1.107(b). Otherwise, the analogy to Glass cannot stand.

Secondly, the Glass compositions are highly viscous formulations. Applicants' compositions, again by virtue of the unique combination of elements, including particle size, are low viscosity compositions. Both of these features, rapid dispersability and low viscosity, are inherent properties associated with the formulation as claimed. One of skill in the art would not be motivated to drastically alter the Glass compositions to compositions having these properties, as suggested by the Office.

Furthermore, contrary to the Office's assertions, MF59 is indeed mentioned in the instant specification. See,

e.g., page 58, line 31; page 59, line 3; page 59, lines 36-39; page 60, line 10; page 60, line 18; and page 60, line 26. Finally, with respect to the data reported in Ott, also questioned by the Office, MF59-0 is MF59 lacking MTP-PE. See, e.g., page 280, lines 8-11 of Ott. In any event, reliance on Ott to show that applicants' unique immunological adjuvants work by a mechanism unlike Glass' is not necessary as such is shown by the Declaration previously submitted.

With respect to Hoskinson, this reference details the combination of polycationic polyelectrolyte immunoadjuvants and oil emulsions. When reviewed in its entirety, Hoskinson actually teaches away from the use of oil-in-water emulsions as adjuvants. Particularly, at column 3, lines 22-24, Hoskinson notes that water-in-oil emulsions are preferable to oil-in-water emulsions. Further, nowhere does Hoskinson suggest the use of an adjuvant having oil droplets substantially all of which are less than 1 micron in diameter as claimed.

Combining Glass and Hoskinson with Idson and Remington does not cure the defects of the primary references. As explained above, Idson does not disclose a preparation falling within the scope of the claims and that acts as an immunological adjuvant. Both Remington and Idson discuss known adjuvants (e.g., Idson, and Freund's adjuvants) and summarize known physical properties of emulsion formulations. There is no suggestion in either of these references that formulations such as described in Hoskinson and Glass could be modified to render applicants' unique compositions. Additionally, there is absolutely no indication that doing so would be successful for producing an adjuvant composition as claimed. Section 2142 of the MPEP sets forth the following basic requirements for *prima*

*facie* obviousness: (1) there must be some suggestion or motivation to modify the references; (2) there must be a reasonable expectation of success (for the modification); and (3) the prior art references must teach or suggest all of the claim limitations. Furthermore, the teaching or suggestion and the reasonable expectation of success must both be found in the prior art, not in applicants' disclosure. Applicants submit that the Office has failed to satisfy each of these criteria and has thus failed to establish *prima facie* obviousness.

Without a suggestion to modify the references evident in the prior art, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). See, also, *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

Thus, applicants submit that the claimed invention is nonobvious over the art and request reconsideration and withdrawal of this ground of rejection.

#### Conclusion

Applicants respectfully submit that the claims as amended define an invention which is novel and nonobvious over the art. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated.

Applicants note that this patent application has been in prosecution since 1989. Since then, numerous Office Actions have issued, the case has been interviewed several times, multiple declarations have been submitted rebutting the Office's rejections, and four Examiners have been assigned to the application, most of which stated new grounds of rejection. Accordingly, applicants are anxious for resolution and welcome any suggestions from the Office in order to advance the case to allowance. Accordingly, should the Examiner note any further matters which she believes may be expedited by a telephone interview, she is urged to contact the undersigned attorney at (650) 325-7812.

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Respectfully submitted,

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